REMARKS

This is response to the non-Final Office action (Paper No. 20070412) mailed 18 April 2007.

Claims 1, 5-9, 21-24 are pending in this application.

No claim has been amended.

No new matter has been added.

I. Claim Rejections – 35 USC §103

A. Claim(s) 1, 7, 8, and 21-24 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Sifis et al. (J Forensic Sci. 2002 May;47(3):589-92) in view of Palmirotta et al. (Journal of Forensic Science. March 1998. (43) 2, 431-434), in further view of Jurka (Nucleic Acids Research. 1993. Vol. 21. No. 9, 2252) as evidenced by Batzer et al. (Journal of Molecular Evolution. 1996. 42, 3-6).

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure.

In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP § 2143 - §2143.03 for decisions pertinent to each of these criteria.

The examiner failed to establish the *prima facie* case of obviousness because the above three basic criteria are not met.

1. The prior art does not suggest the desirability of the claimed invention.

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

Claim 1 recites "said Alu element being more enriched in the human genome than in any non-human primate genome", claim 21 recites "said Alu element being present only in the human genome", and claim 22 recites "a copy number of said predetermined genomic DNA in the human genome being higher than a copy number of said predetermined genomic DNA in any non-human primate genome".

Here, as admitted by the examiner, Palmirotta et al. and Sifis et al. failed to show those features recited in claims 1, 21 and 22. Sifis et al. acknowledged that forensic samples are often contaminated with nonhuman DNA, and they make no attempt to determine the specificity of their intra-Alu amplification, and, in Palmirotta et al., it cannot be determined whether the statue blood originated from humans or from a non-human catarrhine primate.

The examiner argued that "the nature of the methods taught by Sifis and Palmirotta did not necessarily require or even benefit from the amplification of an Alu sequence" which is more enriched in the human genome than in any non-human primate genome, and also argued that it

would not have been necessary to assay an Alu sequence more enriched in the human genome or exclusively contained within the human genome "because there was virtually no chance of inaccurate results due to contaminating non-human primate DNA".

If, as stated by the examiner, there is no benefit from the amplification of an Alu sequence, there is no desirability of combination or modification. In *In re Fritch*, "[c]laims were directed to an apparatus for producing an aerated cementitious composition by drawing air into the cementitious composition by driving the output pump at a capacity greater than the feed rate. The prior art reference taught that the feed means can be run at a variable speed, however the court found that this does not require that the output pump be run at the claimed speed so that air is drawn into the mixing chamber and is entrained in the ingredients during operation. Although a prior art device "may be capable of being modified to run the way the apparatus is claimed, there must be a suggestion or motivation in the reference to do so." 916 F.2d at 682, 16 USPQ2d at 1432.). See also *In re Fritch*, 972 F.2d 1260, 23 USPQ2d 1780 (Fed. Cir. 1992) (flexible landscape edging device which is conformable to a ground surface of varying slope not suggested by combination of prior art references).

Like *In re Fritch*, here, the examiner stated that the prior art references do not require that the Alu element should be more enriched in the human genome than in any non-human primate genome (claim 1) or is present only in the human genome (claim 21), or a copy number of said predetermined genomic DNA in the human genome is higher than a copy number of said predetermined genomic DNA in any non-human primate genome (claim 22). The examiner's reasoning is at most that a statement that modifications of the prior art to meet the claimed invention would have been "well within the ordinary skill of the art at the time the claimed invention was made". ("A statement that modifications of the prior art to meet the claimed

invention would have been "well within the ordinary skill of the art at the time the claimed invention was made" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). See also *In re Kotzab*, 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1318 (Fed. Cir. 2000)." (See MPEP 2143.01.)

Merely showing that there is a general incentive is not enough. ("The general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out." *In re Deuel*, 51 F.3d 1552, 1559, 34 USPQ2d 1210, 1216 (Fed. Cir. 1995).) While a "general incentive" may make an approach "obvious to try" it does not make the invention obvious. "Obvious to try" is not the standard of obviousness under 35 U.S.C. §103. In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1680 (Fed. Cir. 1988).

Since, as admitted by the examiner, the prior art does not show the desirability of the claimed invention, or does not show the motivation to combine the references, a rejection based on a *prima facie* case of obvious is improper.

2. There is no teaching in the prior art references about how to design the primers in order to achieve the same as or similar results to the Sifis et al

If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

In Sifis et al., the SP primer pair was designed to amplify the core sequence of Alu in primate DNA. Protocols were optimized enabling the sensitive detection of DNA from 2.5-

100pg. (See Abstract and co.2, second paragraph at page 590). However, there is no teaching in the prior art references about how to design the primers in order to achieve the same as or similar results to the Sifis et al. The prior art does not show the enablement. The examiner merely argued that Jurka taught that Sb2 is the youngest of all known human Alu subfamilies. Jurka in combination with Sifis et al. and Palmirotta et al. does teach how to make the primers from Sb2 for the PCR protocol from which the amount of the human DNA can be quantitated as described in Sifis et al.

3. Regarding claims 23 and 24, the examiner did not provide sufficient reasoning to establish a prima facie case of obviousness.

Claims 23 and 24 recite that "each of said primers includes a subfamily-specific diagnostic mutation."

With respect to this feature, the examiner merely concluded that "it would have been further prima facie case obvious to a practitioner of ordinary skill in the art at the time of invention to incorporate primers that are complementary to the specific Alu sequence.

For example, as shown in Fig. 2, the primers themselves include the subfamily-specific diagnostic mutations. The *primers* may be designed without including subfamily-specific diagnostic mutations in the primer sequences themselves, even if the *amplified products* amplified by the primers are likely to include subfamily-specific diagnostic mutations. The examiner should provide the reasoning for why a practitioner of ordinary skill in the art at the time of invention would make primers wherein the subfamily-specific diagnostic mutations are incorporated into the primer sequences.

For the foregoing reasons, claims 1, 7, 8, and 21-24 are patentable.

B. Claim 5 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Sifis *et al.* (J Forensic Sci. 2002 May; 47(3): 589-92) in view of Palmirotta *et al.* (Journal of Forensic Science. March 1998. (43) 2, 431-434), in further view of Jurka (Nucleic Acids Research. 1993. Vol. 21. No. 9, 2252), as evidenced by Batzer et al. (Journal of Molecular Evolution, 1996, 42, 3-6), and in further view of Buck *et al.* (BioTechniques. September 1999. 27: 528-536).

The examiner admitted that SEQ ID NOs:3 and 4 are not taught in Sifis et al. and Palmirotta et al, but are contained in Jurka.

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

Here, the examiner's argument is at most that the references can be combined or modified. The examiner did not show the desirability of the combination.

First, unlike the majority of chemical compounds around which the "structural similarity" doctrine emerged, the main technological significance of DNA is wrapped up in its central role in mediating cell physiology. Based on this similarity, biotechnologist has persuasively argued that application of "structural similarity" doctrine to the DNA is inappropriate. (See *In re Bell*, 991 F.2d 781, 784 (Fed. Cir. 1993).

The examiner improperly compared the homologs of the chemical compounds with DNA sequence.

Second, the fact that the sequence is known does not mean that the DNA fragment is obvious.

In *Deuel*. the court acknowledged that the claimed cDNA molecules might be found obvious "if there were prior art, *e.g.*, a protein of sufficiently small size and simplicity, so that lacking redundancy, each possible DNA would be obvious over the protein." *In re Deuel*, 51 F.3d 1552, 1559 (Fed. Cir. 1995); *see also Merck & Co. v. Biocraft Labs.*, 874 F.2d 804, 807 (Fed. Cir. 1989). Citing *Baird*, the court concluded that "[n]o particular one of these DNAs can be obvious unless there is something in the prior art to lead to the particular DNA and indicate that it should be prepared." *Id.* at 1558-59; *see also In re* Bell, 991 F.2d 781, 784 (Fed. Cir. 1993) (reversing a § 103 rejection of a claimed nucleic acid molecule where the prior art disclosed only an amino acid sequence and failed "to suggest which of [the more than 1036 possible nucleotide sequences] is the human sequence").

That is, the court did decide the case based on whether the prior art references "teach or fairly suggest the selection of nucleotide sequence, not on how easily the nucleotide sequences can be written.

Please also note that the examiner's reasoning is similar to the reasoning of the examiner in *In re Baird*. 16 F.3d 380 (Fed. Cir. 1994). In *In re Baird*, the applicant claimed toner compounds comprising a bisphenol A polyester and a dicarboxylic acid selected from the group consisting of succinic acid, glutaric acid, and adipic acid. The prior art reference disclosed a generic formula that can encompass a vast number of diphenols (including bisphenol A) and twenty dicarboxylic acids. The examiner rejected the claim as obvious, reasoning that bisphenol A "may be easily derived from the generic formula of the diphenol in [Knapp] and all the motivation the worker of ordinary skill in the art needs to arrive at the particular polyester of the

instant claim[] is to follow [that formula]." In reversing the Board's rejection, the Federal Circuit found that the reference did not "teach or fairly suggest the **selection** of bisphenol A. A disclosure of millions of compounds does not render obvious a claim to three compounds, particularly when that disclosure indicates a preference leading away from the claimed compounds."

Furthermore, the present case is not whether the partial DNA sequence is obvious over the entire DNA sequence, but whether the process for assaying a product sample uses a certain target sequence among the known DNA sequence.

Here, like *Deuel* and *Bell*, a vast number of target sequences are possible from the known DNA sequence, and the reference did not teach or fairly suggest the **selection** of the sequences of claim 5. That is, the issue is whether the prior art references teach or fairly suggest the selection of nucleotide sequence, not how easily the nucleotide sequences can be written.

Since there is no such a teaching, suggestion or motivation, claim 5 is patentable.

The examiner's attention is also invited to consider the following reference, <http://www.jpo.go.jp/shiryou_e/toushin_e/kenkyukai_e/contents.htm>. In the Comparative Study Report, the following question was given to US PTO:

> **"(1) Y : a structural gene encoding a functional polypeptide, the whole sequence of which is disclosed**
>
> **Y' : a partial DNA fragment of Y**
>
> **Does determination on novelty depend on whether the invention is claimed as "nucleotide" (chemical substance) or "probe" (use) ?"** (See *Id.*)

The US PTO explained, based on the Patent Act, Sections 101, 102, 103 and 112, as follows:

"The entire structural gene would not normally defeat the novelty of a fragment of that gene. However, claim language can be very important. If the fragment were claimed using open ended language such as "comprising," the claimed fragment could lack novelty. Thus, "a nucleotide sequence comprising Y' " would be anticipated by a structural gene that contained Y'.

Under 35 U.S.C. Sec. 103 & 102(e), issued U.S. patents are considered prior art as of their filing date. Consequently, the answer is the same for (a) , (b) or (c).

The answer is the same whether the invention is claimed as a chemical or as a probe. **However, claims directed to a method of using Y', even for open ended claim language such as "a method of using a probe comprising Y' " might be novel."** (Emphasis added. See <ttp://www.jpo.go.jp/shiryou_e/toushin_e/kenkyukai_e/uspto/u50.htm>)
The examiner's position is inconsistent with the US PTO's position in the Report.

Third, with respect to the issue of reasonable expectation of success, the examiner improperly cited Buck. Please note that Buck compares the primers for the exact same 300-bp sequence *in automated DNA sequencing*, using the same PCR reaction condition. If the targets are different and/or the PCR reactions are different, and/or the purposes are different, the PCR primers will not yield the data of the same quality.

The examiner misunderstood Buck's teaching. Buck's teaching can be applied only to the case where the primers are for the exact same sequence in automated DNA sequencing.

For example, unlike Buck's teaching, different primers for the purpose of quantitation of human DNA result in different detection limits and different specificities, and, when there are primate DNA other than human DNA in a sample, different primers may result in different artifact Amplicons from DNA of other species as a result of sequence similarity to SINE elements from other species. Since the purpose of Buck et al. was automated DNA sequencing, these factors were not considered. It should be also noted that the design of a PCR assay may involve tradeoffs among competing objectives, and extensive analysis is required. The result for automated DNA sequencing cannot be applied to the human DNA quantitation method. For example, it is also evidenced by U.S. Pat. No. 7,026,120 disclosing that:

"it is well known that amplification primer sequences can be selected based upon computer comparisons of closely related sequences. Theoretically, sequences selected in this manner effectively should produce copies of the selected target sequence when employed according to nucleic acid amplification principles. Notwithstanding, the theoretical efficacy of sequences selected in the above manner, it is often times true that such sequences do not produce acceptable amounts of amplification product. Unfortunately, this phenomenon is not understood. Accordingly, while primers initially can be screened using computer programs efficacy cannot be adequately determined until such primers are employed in practice." (See Col. 1, lines 45-57.)

Also, the specification in the present application discloses that "the high Tm of the intra-Yb8 Alu-based primers was essential to the elimination of artifact amplicons from DNA of other species as a result of sequence similarity to SINE elements from other species." This problem is not related to Buck wherein the 300 the primers for the exact same 300-bp sequence *in automated DNA sequencing*, using the same PCR reaction condition.

Buck et al. also acknowledged that, in their system, "the plasmid template was selected for absence of sequence extension obstacles and purified by double banding in CsCl-ethidium bromide isopycnic density gradients. Therefore, this template was extremely pure and optimal for sequencing. The primers were similarly highly purified. The reactions were performed in a single high-throughput sequencing facility under tightly controlled conditions. Different results may be obtained using less carefully purified DNA templates with unusual sequences or structures or in less rigorously controlled sequencing operations." (See page 535, last paragraph to page 536, first paragraph in Buck et al., emphasis added.) Accordingly, the teaching of Buck et al. can be applied only to the same reaction condition as described in Buck et al.

The primers of claim 5 are not solely for automated DNA sequencing of a 300-bp test sequence as disclosed in Buck et al. Accordingly, it cannot be applied to the present application.

For the foregoing reasons, the examiner failed to establish a prima facie case of obviousness.

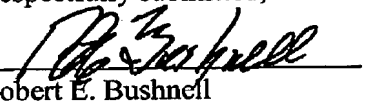
C. Claim 9 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Sifis et al. in view of Palmirotta et al., in further view of Jurka as evidenced by Batzer et al. as applied to claim(s) 1, 7, 8, 21, and 22 above, and in further view of Gelmini et al. (Clinical Chemistry. 1997. 43:5, Pages 752-758).

Claim 9 depends from claim 1. Since claim 1 is patentable, claim 9 is also patentable.

No fees are incurred by this Response.

In view of the above, all claims are submitted to be allowable and this application is believed to be in condition to be passed to issue. Reconsideration of the rejections is requested. Should any questions remain unresolved, the Examiner is requested to telephone Applicant's attorney.

Respectfully submitted,



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Folio: P56885
Date: 7/17/2007
I.D.: REB/JHP